THE MECHANISM OF ADAPTING WHITE MICE TO A HYPERCAPNIC GASEOUS ENVIRONMENT

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ABSTRACT: We cite data on studying the influence of a hypercapnic gaseous environment (3 - 10% CO_2) on the functional condition of the central nervous system. The index of the reaction of the central nervous system to hypercapnia was the sensitivity of the animals to narcotics (ether, intranarcon). We established the dependence of the phase changes in the functional interrelationships of the cortex in the subsutaneous formation of the central nervous system on the degree of hypercapnia and the duration of adaptation.

Study of the mechanisms of adapting the organism to prolonged residence in a changed gaseous environment is of great practical significance in the development of systems of survival relative to the problems of aviation, astronautics, submarines, etc. Special attention must be paid to this program in studying the reaction of the organism to prolonged breathing of hypercapnic gaseous mixtures.

The character of the physiological changes, observed as a results of the effect of different degrees of hypercapnia, has been studied rather fully [1,4,6]. Here it has been established that the numerous physiological phenomena which appear with breathing of hypercapnic gas mixtures are due to the suppression of the effect of carbon dioxide on the various links of the nerve regulation [3, 5,8,12,13,15]. We must show that the literature data concerning the mechanisms of adaptation to hypercapnia are quite contradictory; this can apparently be explained by the different methodological approaches used by the authors, and also by an insufficient accounting of the time of effect of the carbon dioxide gas mixtures.

In the present paper we studied the character of the changes in the functional condition of various parts of the central nervous system of animals in the process of adaptation to various degrees of hypercapnia. As the criteria of the functional condition of the nervous system we used signs of change in the reaction of the animals to narcotic preparations. Such a methodological appraoch was found to be justified, since in studying the characteristics of the reaction of the organism to medicinal compounds under conditions of /205
a changed gas environment, we solved problems which are significant in the theoretical and practical sense [2,7,15].

METHOD

The investigations were made on 320 white male rats weighing 18 - 25 g. The intervals between the experiments on the same animals was seven days. The animals were subjected to the effect of a hypercapnic gas mixture, containing 3 - 5 or 8 - 10% carbon dioxide and an ordinary amount of oxygen. The artificial gas atmosphere was created in a special chamber with a volume of 50.4 liters, ventilated with a gas mixture from a tank. The composition of the gas mixture in the chamber was controlled with a complex gas analyzer from the firm "Godart". The reaction to the narcotics (ether and intranarcon) was studied in the control animals and in the experimental animals subjected to the effect of different degrees of hypercapnia for a period of 1 - 4 hours.

The ether narcotic was given in a hermetically sealed excicca-tor with a volume of 9.1 liters simultaneously to 10 animals (5 control and 5 experimental) for a period of 15 minutes with a concentration of ether vapors of 300 mg/liter. The intranarcon was injected intraperitoneally in a dose of 150 mg/kg (0.1 ml solution per 10 g of animal weight).

We recorded the time of onset and the total duration of the narcosis in stages III-IV after Schoen [19] and also the duration of the reverse development of narcosis after cessation of the narcotization (in the experiments with ether). The experimental material was anlyzed statistically [11] and the data of the narcotic effect of the compounds in the control and the experimental groups of animals were compared.

RESULTS

Observation of the reactions of the animals during their residence in the hypercapnic gas environment did not reveal any substantial changes in their behavior in comparison with the control animals. At the end of the first hour of breathing the hypercapnic gas mixture the animals as a rule quieted down and the notive reactions of "pursuit" disappeared. No pronounced differences were observed in the behavior of the animals as a function of the concentration of carbon dioxide in the inhaled gas mixture. However, the reaction of the mice to the pharmacological agents taken underwent changes associated both with the concentration of carbon dioxide in the gas misture and with the duration of residence of the animals in it.

Such data concerning the raaction of animals to ether for different periods of adaptation to a hypercapnic gas atmosphere are shown on Table 1. As is obvious from this material, the narcotic state in the experimental mice subjected to the effect of a gas mixture with 3 - 5% carbon dioxide content was developed approximately the same as in the control animals (from 94.2 to 109.8%). The /206
total duration of narcosis in this series of experiments (during the first 2 hours of residence in the artificial gas atmosphere)

practically did not change. However, with narcotization in the later periods toward the third hour a slight relative decrease was noted in the total duration of narcosis (84.6%), and by the fourth

TABLE 1. SEVERAL CHARACTERISTICS OF DURATION OF ETHER NARCOSIS IN WHITE MICE AFTER BREATHING HYPERCAPNIC GAS MIXTURES (AVERAGE DATA).

Sign of narcotic effect	CO_2 in gas mixture, %	Statistical Index	Time of breathing gas mixture, hour							
			1		2		3		4	
			cont.	exp.	cont.	exp.	cont.	exp.	cont.	exp.
Times of onset of narcosis from beginning of narcotization, min.	3—5	*M*.....	7.65	8.03	7.62	7.55	7.34	8.05	8.15	7.69
		% of control	—	104.8	—	99.0	—	109.8	—	94.2
	8—10	*M*.....	8.2	8.2	8.4	9.1	8.4	9.3	8.6	9.6
		% of control	—	100	—	108.2	—	110.6	—	111.5
Total duration of narcosis stages III-IV, min.	3—5	*M*.....	12.5	11.9	12.3	13.1	12.9	10.9	10.8	12.35
		% of control	—	95.5	—	106.1	—	84.6	—	113.9
	8—10	*M*.....	9.8	11.3	10.5	9.2	11.6	12.3	11.9	9.9
		% of control	—	115.4	—	87.4	—	106	—	83.3
Times of inverse development of narcosis after end of narcotization, min.	3—5	*M*.....	4.97	4.95	5.48	5.7	5.35	4.02	4.31	5.05
		% of control	—	99.8	—	104	—	75.2	—	117
	8—10	*M*.....	3.1	4.53	4.35	4.5	5.0	6.9	5.42	4.67
		%of control	—	146	—	103.2	—	138	—	86.4

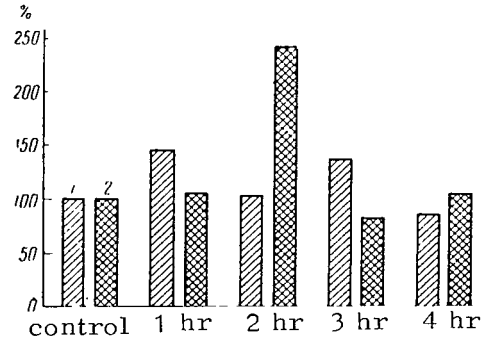
hour, an increase up to 113.9%. The time of the inverse development of narcosis after end of narcotization varied in parallel with the changes in its total duration. /207

Thus, the changes in the reaction with respect to ether in the experiments with prolonged residence of the animals in an atmosphere of 8 - 10% carbon dioxide differed in manifestation and earlier development.

Taking into account the characteristics of the pharmacological effect of ether, having primarily a cortical effect, it was interesting to compare the results obtained with the data concerning the reaction of the animals under the same methodological experimental conditions to intranarcon with the point of application primarily in the region of the subcutaneous formations of the brain. Data on the reaction of mice to intranarcon are given on Table 2.

As is obvious from the data in the table, the average duration of the intranarcon narcosis in the white mice was reliably increased ($t > 1.96$) after two hours of residence in hypercapnic gas environment, and in the other periods practically did not differ from the control data. Here the change in the reaction to the compound was expressed to a larger degree with breathing of the animals of an 8 - 10% carbon dioxide gas mixture (243%) and to a lesser degree with breathing of a 3 - 5% CO_2 mixture. /208

Based on the above positions concerning the characteristics of the effect of medicinal compounds as a function of the original functional state of the organism [9] we may assume that the narcotic effect of the compound is increased at the expense of the change in the functional mutual relationships between the cortex and the subcortex with the main development of the processes of slow down in these or other structures.



Comparative Data on Changes in the Reaction of White Mice to Narcotics Under the Influence of Prolonged Residence in a Gas Environment with 8 - 10% Carbon Dioxide Content: 1. Duration of Inverse Development of Ether Narcosis; 2. Total Duration of Intranarcon Narcosis. Average Data are in Percents of Control.

Change in the reaction to narcotics in the process of adaptation of animals to a 3 - 5% carbon dioxide gas mixture permits the assumption of a high sensitivity of the sucortical structures of the brain to the effect of carbon dioxide. In fact an increase was observed earlier in the sensitivity to the intranarcon (after two hours)

which may indicate the development of retarding processes in the subcortical formations. Then, after 3 hours, changes were observed also in the reaction of the cerebral cortex to ether.

Experiments with the use of 8-10% carbon dioxide gas mixture had several qualitative differences (see the Figure). Thus under these conditions the first changes in the reaction of the central nervous system appeared from the side of the cortex (after one hour), and then the dynamics of the change in sensitivity to the narcotics was the same as in the experiments using 3 - 5% CO_2. The obtained facts can be explained by the fact that the specific retarding effect of the carbon dioxide on the central nervous system has different points of application as a function of its concentration in the inhaled gas mixture. Apparently the small concentrations (3 - 5%) first of all produce functional changes in the region of the subcortical formations, which appear as changes both in the humoral and in the nerve regulation of breathing and blood circulation [5,6,16]. The higher concentrations of carbon dioxide (8 - 10%) are characterized by the suppression of the effect on the cortical structures of the brain as a result of the appearance of its narcotic properties [3,6,10,14,17,18]. /209

TABLE 2. DURATION OF INTRANARCON NARCOSIS IN WHITE MICE IN BREATHING A HYPERCAPNIC GAS MIXTURE, MIN. (AVERAGE DATA).

Time of Residence in Gas Environment, hours	Statistical Index	CO_2 Content in Gas Mixture, %: 3—5 Cont.	3—5 Exp.	8—10 Cont.	8—10 Exp.
1	$M \pm m$	65,4±14,95	76,2±18,2	51,25±8,96	54,22±10,98
	% of control	—	116,3	—	105,7
	t	—	0,46	—	0,21
2	$M \pm m$	84,9±10,1	129,2±15,82	30,0±7,55	72,9±10,68
	% of control	—	152,3	—	243,0
	t	—	2,31	—	2,85
3	$M \pm m$	107±13,74	105±17,96	89±12,3	73,8±9,34
	% of control	—	98,2	—	83,1
	t	—	0,09	—	0,98
4	$M \pm m$	90,4±17,1	79,5±13,16	49,1±11,4	51,6±16,0
	% of control	—	88,0	—	105,0
	t	—	0,50	—	0,12

t = criteria of reliability of the difference in average values.

It should be shown that according to the data obtained, in the process of adaptation of the white mice to hypercapnia, approximately on the fourth hour a tendency was observed to normalization of the cortico-subcortical interrelationships in the central nervous system. Whether this serves as a sign of future adaptation to changed conditions of the gas environment or whether it reflects only the transitional period to the next phase change of the functional tonus of the various parts of the nervous system will necessitate special experiments.

Thus, in conclusion let us note that the methods of studying /210 the changes in the functional condition of the central nervous system by investigating the characteristics of the reaction to pharmacologicial compounds with different points of application permitted obtaining objective data on the different mechanism of the functional changes in the organism as a function of the concentration and duration of the effect of the carbon dioxide gas mixtures.

CONCLUSIONS

1. Prolonged residence in a hypercapnic gas environment is accompanied by phase changes in the reaction of the animals to narcotic remedies.

2. Change in the reaction to narcotics indicates a disruption in the functional interrelationships between the cortex and the subcortical structures of the brain.

3. Adaptation of animals to a hypercapnic gas environment with 3 - 5% carbon dioxide content is accompanied by the appearance of signs of retardation first of the subcortical formations.

4. A prolonged effect of the gas environment with 8 - 10% carbon dioxide is associated in first order with the cortical structures of the brain.

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